EXTENDED RELEASE PHARMACEUTICAL TABLET OF METFORMIN

RELATED APPLICATIONS

[0001] This application is a continuation-in-part of application Ser. No. 10/309,193, filed December 4, 2002, which is a continuation-in-part of application Ser. No. 10/005,387, filed December 4, 2001 both of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to an extended release pharmaceutical tablet containing metformin as an active substance.

BACKGROUND OF THE INVENTION

[0003] For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the duration of the treatment. Providing dose size and frequency of administration are correct, therapeutic 'steady-state' plasma concentrations of a drug can be achieved promptly and maintained by the repetitive administration of conventional peroral dosage forms. However, there are a number of potential limitations associated with conventional peroral dosage forms.

[0004] These limitations have led pharmaceutical scientists to consider presenting therapeutically active molecules in 'extended-release' preparations. In reality the scientists were attempting to take the control of medication away from the patient, and to some extent the physician, and to place it in the drug delivery system.

[0005] Oral ingestion is the traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled-release (CR) delivery systems provide a uniform concentration/amount of the drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic

range, which minimizes side effects and also reduces the frequency of administration. CR products are formulations that release active drug compounds into the body gradually and predictably over a 12- to 24-hour period and that can be taken once or twice a day. Typically, these products provide numerous benefits compared with immediate-release drugs, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience, and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market.

[0006] Over the years many drug delivery systems have been developed with the aim of eliminating the cyclical changes in plasma drug concentration seen after the administration of a conventional delivery system. A variety of terms have been used to describe these systems: delayed release, repeat action, prolonged release, sustained release, extended release, controlled release and modified release. It is interesting to note that the USP considers that the terms controlled-release, prolonged release, sustained release and extended-release are interchangeable.

[0007] Extended-release tablets have been described in the prior art and many methods have been used to provide extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

[0008] Osmotic systems, for example, utilize osmotic pressure as the driving force for the delivery of drugs. In its simplest design, it consists of an osmotic core (a drug with or without an osmagent), which is coated with a semipermeable membrane, and a delivery orifice is created with a mechanical or laser drill. When the dosage form comes in contact with water, water is imbibed because of the resultant osmotic pressure of the core and the drug is released from the orifice at a controlled rate. This system, known as elementary osmotic pump (EOP), was first developed by the Alza Corporation and is described in for example US Pat. Nos. 3,845,770, 3,916,899, 4,034,758, 4,077,407, 4,783,337 and 5,071,607. US Pat. No. 6,099,859, for example, teaches an osmotic device wherein the active agent, metformin hydrochloride, is released from a core surrounded by a semipermeable membrane, which is impermeable to the active agent. The semipermeable

membrane contains within it a flux enhancer, which, according to the disclosure, can be a water-soluble material or an enteric material. The flux-enhancing agent dissolves or leaches from the semipermeable membrane to form paths in the semipermeable membrane for the fluid to enter the core and dissolve the active ingredient. The semipermeable membrane may also have an orifice formed by a mechanical or laser drill.

[0009] A number of modifications of this system are available today, like the push-pull osmotic pump, which is a bilayer tablet and is suitable for the delivery of highly or poorly water-soluble drugs. The upper layer consists of a drug along with osmotic agents. The lower layer consists of polymeric osmotic agents. The tablet is coated with a semi-permeable membrane, and a delivery orifice is created similar to that of an EOP. The push-pull osmotic system is described in for example US Pat. Nos. 4,612,008 and 5,082,668. Examples of the push-pull osmotic system products developed by Alza Corporation include Ditropan XL, Glucotrol XL and Procardia XL. A major disadvantage of the above-described systems is that mechanical or laser drilling is capital intensive. Also, the size of the hole is critical. Further, the integrity and consistency of the coating is essential. If the coating process is not well controlled there is a risk of film defects, which could result in dose dumping and the film droplets must be induced to coalesce into a film with consistent properties.

[0010] MODAS or Multiporous Oral Drug Absorption System developed by Elan Corporation is surrounded by a non-disintegrating, timed-release coating, which after coming in contact with gastrointestinal fluid is transformed into semipermeable membrane through which the drug diffuses in a rate-limiting manner. The tablet consists of a core of active drug plus excipients. This is then coated with a solution of insoluble polymers and soluble excipients (pore-forming agents). After ingestion, the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer, thereby forming a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water-soluble drug. This fluid passes through these channels into the core, dissolves the drug, and a resultant solution of drug diffuses out in a controlled manner to the outside. The addition of excipients, such as buffers can help produce a microenvironment within the tablet that facilitates more predictable release rates

and absorption. The MODAS is described in for example US Pat. No. 5,505,962. A disadvantage of the MODAS is that the coating, since it requires a pore forming agent, cannot provide a uniform coating and therefore the release rate may not be uniform from one tablet to another.

[0011] In addition to osmotic principles, numerous other approaches also exist for the delivery of drugs in a controlled manner. US Pat. No. 5,955,106, for example, describes a pharmaceutical composition containing metformin as an active substance and a hydrocolloid-forming agent as a retardant. The use of hydrocolloid-forming agents as retardants is based on the property of the hydrocolloid-forming agent to swell and form a gel matrix when it is contacted with a release medium or digestive juices. The matrix erodes to release the active substance. The interaction between the amount of hydrocolloid-forming agent and the degree of viscosity determines the time course of release. Other non-osmotic approaches include for example CEFORM® microsphere technology (Biovail Corporation International), Dual Release Drug Absorption System (DUREDAS, Elan Corporation), Geomatrix™ technology (Skye Pharma Plc., USA), and Granulated Modulating Hydrogel System (GMHS, Andrx Pharmaceuticals).

[0012] Several metformin formulations are now available on the market, but these existing formulations suffer from the disadvantages described above. Therefore, there remains a need for an improved pharmaceutical composition for delivering metformin from the pharmaceutical composition at a sustained rate after a desired time delay or a controlled onset of release while avoiding the disadvantages of the presently known compositions.

SUMMARY OF THE INVENTION

[0013] In accordance with an aspect of the present invention, there is provided an extended release pharmaceutical tablet comprising:

(i) a core comprising by weight, based on the core weight, about 70% to about 99% metformin and pharmaceutically acceptable excipients; and

(ii) a coating surrounding said core, wherein said coating is permeable to metformin,

said tablet exhibiting a dissolution profile such that after about 2 hours, from about 7% to about 60% of the metformin is released; after about 4 hours, from about 15% to about 90% of the metformin is released; after about 8 hours, from about 50% to about 100% of the metformin is released; after about 12 hours, more than about 75% of the metformin is released.

[0014] In a preferred embodiment, the invention provides a coating consisting essentially of a water-insoluble, water-permeable film-forming polymer; a water-soluble polymer and a plasticizer and is free of monomeric pore-forming agent. Preferably, the coating consists essentially by weight, based on the coating weight, from about 20% to about 85% of water-insoluble, water-permeable film-forming polymer, from about 10% to about 75% of water-soluble polymer and from about 3% to about 40% plasticizer. Preferably, the coating consists essentially by weight, based on the coating weight from about 50% to about 85% of water-insoluble, water-permeable film-forming polymer, from about 10% to about 35% of water-soluble polymer and form about 3% to about 15% of plasticizer. Preferably, the water-insoluble, water-permeable polymer is ethylcellulose, and the water-insoluble polymer is polyvinylpyrrolidone. A preferred plasticizer is selected from the group consisting of stearic acid and dibutyl sebacate. Preferably, the pharmaceutical excipients comprise glyceryl behenate, polyvinylalcohol and silicon dioxide.

[0015] The core may further comprise an expanding agent. If an expanding agent is present, it is present preferably in an amount from about 3% to about 25% of the core dry weight. The expanding agent is preferably a non-hydrocolloid. More preferably, the non-hydrocolloid is crospovidone.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The present invention will be further understood from the following detailed description with references to the following drawings.

[0017] **FIG. 1** is a graph depicting the dissolution profile of the formulations described in Example 4.

[0018] **FIG. 2** is a graph depicting the dissolution profile of the formulations as described in Example 4A.

[0019] **FIG. 3** is a graph depicting the dissolution profile of the formulations as described in Example 4B

[0020] **FIG. 4** is a graph depicting the dissolution profile of a formulation having a core of the present invention with or without the expanding agent Crospovidone coated with the semi-permeable membrane as taught in US Patent No. 6,099,859.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The invention provides a tablet comprising a core and a coating. The core includes metformin or a pharmaceutically acceptable salt thereof and conventional excipients, for example a lubricant, and a binder and/or a filler, and optionally a glidant. Optionally the tablet may contain other pharmaceutically acceptable excipients in the core and/or the coating.

[0022] Examples of commonly known lubricants include stearic acid, magnesium stearate, glyceryl behenate, stearyl behenate, talc, mineral oil (in polyethylene glycol), and sodium stearyl fumarate etc. Glyceryl behenate is the preferred lubricant. Examples of binders include water-soluble polymer, such as modified starch, gelatin polyvinylpyrrolidone, polyvinylalcohol (PVA), etc. The preferred binder is polyvinylalcohol. Examples of fillers include lactose, microcrystalline cellulose, etc., the latter being preferred. An example of a glidant is silicon dioxide (Aerosil® of Degussa). The above binders, lubricants, fillers glidants, and any other excipient that may be present can further be found in the relevant literature, for example in the Handbook of Pharmaceutical Excipients. The relative amounts of ingredients in the core are preferably as follows. The proportion of metformin in the core may vary between about 70% and about 90%, preferably about 85% and about 98%, of the core dry weight. The proportion of lubricant and/or glidant in the core may vary between about 0.3% and about 10%, preferably about 0.5% to about 3%, of the core dry weight. The proportion of binder or filler in the core may vary between about 0.5% and about 25%, preferably about 1% to about 10%, of the core dry weight.

[0023] The core may further comprise, according to one embodiment of the invention, an expanding agent. The expanding agent may be either a hydrocolloid or a non-hydrocolloid. The expanding agent will lead to an expansion of e.g. from about 10% to about 35% vol., especially from about 15% to about 30% vol. This expansion will allow the drug to stay longer in the stomach in fed conditions (metformin is generally to be taken in fed conditions, since the metformin absorption mechanism is considered to be mainly through the intestine walls). An example of a hydrocolloid agent is Na starch glycolate (Primogel®); any agent that swells with water can also be used e.g., known disintegrant agents. Suitable non-hydrocolloid agents are for example insoluble polyvinylpolypyrrolidones such as Crospovidone (Kollidon CL®), polacrilin potassium (Amberlite® IRP 88) and microcrystalline cellulose (Avicel®). The preferred expanding agent is Crospovidone. The proportion of expanding agent, when one is present, in the core may vary between from about 3% and about 25%, preferably from about 5% to about 20%, of the core dry weight.

[0024] Tablets according to the invention can be prepared through various manufacturing processes known in the art. For example, a manufacturing process for preparing a core according to the invention is as follows. Metformin is first granulated with a binder, in a granulator, preferably but not necessarily a fluidized bed granulator. The binder is first dissolved or dispersed in a suitable solvent, preferably water. The solution or suspension of binder is then sprayed onto the drug in a granulator, e.g. fluidized bed granulator. For example, fluidized bed granulators manufactured by Glatt (Germany) or Aeromatic (Switzerland) can be used for this operation. Another exemplary process involves the use a conventional or high shear mixer to precede granulation. If necessary, the drug can be mixed with a filler, prior to the granulation step. Granules once dried can be mixed with the other excipients, especially with the lubricant and the expanding agent if present, but also with glidants and any other excipient suitable to improve processing. The mixture of granules (preferably with lubricant), and optionally glidant is pressed into tablets. Alternatively, the active ingredient and lubricant and/or glidant and/or expanding agent can be mixed with a suitable filler and compressed into tablets (the expanding agent may also be added at that stage). Also, it is possible to mix the active ingredient and the

lubricant (e.g. glyceryl behenate), and the expanding agent if present, in a granulator, e.g., a fluidized bed granulator, and then to press the resulting granules into tablets. Tablets can be obtained by standard techniques, e.g. on a (rotary) press (for example Manesty Betapress®) fitted with suitable punches. The resulting tablets are hereinafter referred as tablet cores.

[0025] These tablet cores are then coated with a coating designed to achieve an extended release of metformin. The coating comprises a water-insoluble, water-permeable film-forming polymer, together with a plasticizer and a water-soluble polymer. The coating disclosed herein is permeable to metformin. It is well known in the art that varying the ratios of the water-insoluble, water-permeable film-forming polymer:water-soluble polymer can alter the permeability of the coating and hence alter the release of metformin. Additionally, the presence or absence of an expanding agent in the tablet cores will also influence the permeability of the coat to metformin. Accordingly, those of skill in the art will appreciate that the ratio of water-insoluble, water-permeable film-forming polymer:water-soluble polymer:plasticizer may have to be changed depending on the presence or absence of an expanding agent in the tablet core. Plasticizers are used to make the coat elastic and pliable. The amount and choice of the plasticizer contribute to the hardness of the final tablet and may even affect its dissolution or disintegration characteristics, as well as its physical and chemical stability. The presence of an expanding agent in the tablet core will increase the mechanical pressure exerted on the coat and accordingly the amount of plasticizer in the coat should be increased to make the coat more pliable as the coat will otherwise break. The ratio of water-insoluble, water-permeable film-forming polymer:water-soluble polymer:plasticizer taught herein is permeable to metformin and is free of pore-forming agent.

[0026] The water-insoluble, water-permeable film-forming polymer can be a cellulose ether, such as ethylcellulose, a cellulose ester, such as cellulose acetate, etc. A preferred film-forming polymer is ethylcellulose (available from Dow Chemical under the trade name Ethocel®). The plasticizer can be an ester such as a citrate ester or dibutyl sebacate, an oil such as castor oil, a polyalkyleneglycol such as polyethyleneglycol of various molecular weights, a fatty acid such as stearic acid. The preferred plasticizers are dibutyl

sebacate and stearic acid. The water-soluble polymer can be, but is not limited to, water-soluble cellulose ethers, vinylic polymers and combinations thereof. The water-soluble cellulose ethers include, but are not limited to, methylcellulose, hydroxypropylmethylcellulose, non-ionic water-soluble cellulose ethers and combinations thereof. The non-ionic water-soluble cellulose ethers include, but are not limited to, hydroxypropylcellulose, hydroxyethylcellulose and combinations thereof. The vinylic polymers include, but are not limited to, polyvinyl alcohol, polyvinylpyrrolidone and combinations thereof. Polymers that are soluble in both water and alcohol, or in mixtures of water and alcohol also fall within the scope of the invention described herein. Polymers soluble in both water and alcohol suitable for use in the invention include, but are not limited to, hydroxypropylcellulose and polyvinylpyrrolidone. Polymers soluble in mixtures of water and alcohol include, but are not limited to, hydroxypropylmethylcellulose. The preferred water-soluble polymer is polyvinylpyrrolidone. Some other excipients can be used in the coating, as for example acrylic acid derivatives (for example those available from Roehm Pharma under the trade name Eudragit®), pigments, etc. The relative amounts of ingredients in the coating are preferably as follows. The proportion of water-insoluble, water-permeable polymer (e.g. ethylcellulose) in the coating may vary between about 20% and about 85% of the coating dry weight. The proportion of water-soluble polymer (e.g. polyvinylpyrrolidone) in the coating may vary between about 10% and about 75% of the coating dry weight. The proportion of plasticizer (e.g. stearic acid) in the coating may vary from about 3% and about 40% of the coating dry weight. The relative proportions of the ingredients, notably the ratio of water-insoluble, water-permeable film-forming polymer to water-soluble polymer and to plasticizer, can be varied depending on the release profile to be obtained (a more extended release is generally obtained with a higher amount of water-insoluble, water-permeable film forming polymer) and the presence of an expanding agent in the core (which usually leads to more plasticizer and less water-insoluble, water-permeable film forming polymer).

[0027] For example, the following are preferred proportions of water-insoluble, water-permeable film-forming polymer:water-soluble polymer:plasticizer:

- without any expanding agent: 50-85:10-35:3-15;
- with an expanding agent: 20-50:35-75:15-40.

[0028] The coating process can be as follows. Ethylcellulose, dibutyl sebacate (or stearic acid) and polyvinylpyrrolidone are dissolved in a solvent such as ethanol. The resulting solution is sprayed onto the tablet cores, using a coating pan or a fluidized bed apparatus. The weight ratio of coating/tablet core is comprised e.g. between about 1:50 and about 5:10, preferably between about 2:100 and about 20:100, e.g. from about 5:100 to about 10:100.

[0029] The tablet comprises an amount of metformin that can vary within broad limits, such as from about 400mg to about 2000mg. With exemplary ranges being about: 500mg-2000mg; 600mg–1800mg; 700mg–1500mg; 800mg–1300mg or 900mg–1100mg. It is preferred that the tablet comprises 500mg, 750mg or 1000mg of metformin. Surprisingly, it was discovered that the above formulation did not lead to any degradation of metformin through no stabilizer was present in the formulation. Stability studies were conducted in an oven, under the storage conditions described in the US Pharmacopoeia 23rd edition, page 1961. Under these conditions no significant change in drug potency could be seen. Also, it was surprisingly discovered that the above formulation did provide an extended (sustained) release formulation although no monomeric pore-forming agent was present in the coating.

[0030] The invention thus provides a metformin extended release tablet free of stabilizer and free of pore-forming agent, exhibiting a dissolution profile such that after 2 hours, form about 7% to about 60% of the metformin is released; after about 4 hours, from about 15% to about 90% of the metformin is released; after about 8 hours, form about 50% to about 100% of the metformin is released; after about 12 hours, more than about 75% of the metformin is released.

[0031] According to one embodiment, the dissolution profile is such that after about 2 hours, from about 10% to about 40% of the metformin is released; after about 4 hours, from about 20% to about 65% of the metformin is released; after about 8 hours, from about 50% to about 100% of the metformin is released; after about 12 hours, more than about 75% of the metformin is released. According to another embodiment, the dissolution

profile is such that after about 2 hours, from about 40% to about 60% of the metformin is released; after about 4 hours, from about 65% to about 90% of the metformin is released; after about 8 hours, from about 85% to about 100% of the metformin is released; after about 12 hours, more than about 90% of the metformin is released.

[0032] Examples of preferred metformin tablets according to the invention include a tablet composition comprising:

(i) a core comprised of metformin, polyvinylalcohol, silicon dioxide and glyceryl behenate; and

(ii) a coating comprised of ethylcellulose, polyvinylpyrrolidone and stearic acid or dibutyl sebacate.

[0033] Another preferred tablet composition is one in which the core additionally comprises an expanding agent. The expanding agent is preferably a non-hydro colloid expanding agent. Preferably, the non-hydro colloid-expanding agent is an insoluble polyvinylpolypyrrolidone such as Crospovidone (Kollidon-CL®).

EXAMPLES

[0034] The following examples illustrate the invention without limiting it, where the amounts are given per dosage form.

EXAMPLE 1A

[0035] The following formulation is prepared:

Ingredients	Amount (mg)
Metformin	1000.00
Polyvinylalcohol (PVAe)	25.00
Silicon Dioxide	20.00
Glyceryl behenate	21.00
Total (dry weight)	1066.00

[0036] Metformin and silicon dioxide are placed in a fluidized bed apparatus. An aqueous PVA solution (at 1% by weight) is sprayed to get granules. The apparatus is a Glatt GPCG1, operated with the following parameters:

Air flow (m^3/h)	100-110 m^3/h
Liquid flow (g/min)	6-7 g/min
Inlet temperature	65^{oC}
Spraying pressure	2.8 bar

[0037] The granules thus obtained are subsequently dried. Then they are passed through a sieve (1 mm mesh) and glyceryl behenate is weighed, added and blended in a drum mixer (Turbula T2C, Bachoffen, Switzerland). The resulting mixture is pressed into tablets (7 mm diameter and 7 mm curvature) with average hardness being between 60 and 120 N. These tablet cores are then coated with the following formulation:

Ingredients	Amount (mg)
Tablet Cores	1066.00
Ethocel PR100 (ethylcellulose)	42.63
Kollidon 90F (povidone USP)	14.98
Stearic acid	6.39
Total (dry weight)	1130.00

[0038] Ethocel, povidone and stearic acid are first dissolved in denatured alcohol (550g). The coating solution is then sprayed onto the tablet cores in a coating pan (Vector LCDS), with the following spraying parameters:

Air flow (m^3/h)	100-110 m^3/h
Liquid flow (g/min)	6-7 g/min
Inlet temperature	65^{oC}
Spraying pressure	2.8 bar

Stability data:

[0039] Storage conditions: conforms to USP 23 guideline (25°C and 60% relative humidity and 40°C and 75% relative humidity). The results show that the metformin composition of this example is stable.

EXAMPLE 1B

[0040] Example 1A is reproduced according to the same manufacturing process described above, with the following formulation in the core:

Ingredients	Amount (mg)
Metformin	500.00
Polyvinylalcohol (PVAe)	12.50
Silicon Dioxide	10.00
Glyceryl behenate	10.50
Total (dry weight)	533.00

The coating has the following formulation:

Ingredients	Amount (mg)
Tablet Cores	533.00
Ethocel PR100 (ethylcellulose)	26.50
Kollidon 90F (povidone USP)	9.55
Stearic acid	3.95
Total (dry weight)	573.00

The stability results show that the metformin composition of this example is stable.

EXAMPLE 2A

[0041] Example 1A reproduced, but with the following coating formulation:

Ingredients	Amount (mg)
Tablet Cores	1066.00
Ethocel PR100 (ethylcellulose)	41.33
Kollidon 90F (povidone USP)	16.47
Stearic acid	6.20
Total (dry weight)	1130.00

The stability results show that the metformin composition of this example is stable.

EXAMPLE 2B

[0042] Example 1B is reproduced, but with the following coating formulation:

Ingredients	Amount (mg)
Tablet Cores	533.00
Ethocel PR100 (ethylcellulose)	25.24
Kollidon 90F (povidone USP)	7.97
Stearic acid	3.79
Total (dry weight)	570.00

The stability results show that the metformin composition of this example is stable.

EXAMPLE 3A

[0043] The following formulation is prepared:

Ingredients	Amount (mg)
Metformin	1000.00
Polyvinylalcohol (PVAe)	25.00
Silicon Dioxide	25.00
Glyceryl behenate	23.00
Primogel NF 17	100.00
Total (dry weight)	1173.00

[0044] The same procedure as described in example 1A is followed, except that Primogel® is added at the same time as glyceryl behenate.

The tablet cores thus obtained are then coated with the following formulation:

Ingredients	Amount (mg)
Tablet Cores	1173.00
Ethocel PR100 (ethylcellulose)	30.60
Kollidon 90F (povidone USP)	37.40
Dibutyl sebacate	17.00
Total (dry weight)	1258.00

[0045] The same procedure as in example 1A is followed, except that stearic acid is replaced with dibutyl sebacate. The stability results show that the metformin composition of this example is stable.

EXAMPLE 3B

[0046] Example 3A is reproduced according to the same manufacturing process as Example 1A with the following formulation in the core:

Ingredients	Amount (mg)
Metformin	500.00
Polyvinylalcohol (PVAe)	12.50
Silicon Dioxide	10.00
Glyceryl behenate	23.00
Primogel NF 17	50.00
Total (dry weight)	533.00

The coating has the following formulation:

Ingredients	Amount (mg)
Tablet Cores	533.00
Ethocel PR100 (ethylcellulose)	21.25
Kollidon 90F (povidone USP)	21.25
Dibutyl sebacate	10.60
Total (dry weight)	636.10

The stability results show that the metformin of this example is stable.

EXAMPLE 4

[0047] The following formulation is prepared:

Ingredients	Amount (mg)
Metformin	1000.00
Polyvinylalcohol (PVAe)	25.00
Silicon Dioxide (Aerosil® 200)	25.00
Glyceryl behenate (Compritol® 888 ATO)	23.00
Crospovidone (Kollidon CL ®)	50.00
Purified water	520
Total weight (dry weight)	1123.00

The coating has the following formulation:

Ingredients	Amount (mg)		
	Lot #		
	3508	3517	3541
Tablet Cores	1123.00	1123.00	1123.00
Ethocel 100 STD Premium (ethylcellulose)	45.33	46.04	47.46
Kollidon 90F (povidone USP)	25.5	24.79	23.37
Dibutyl sebacate	14.17	14.17	14.17
Ethyl Alcohol 200 Proof	869.25	869.25	869.25
Isopropyl Alcohol 99% USP	45.75	45.75	45.75
Total (dry weight)	1208.00	1208.00	1208.00

The stability results show that the metformin of this example is stable.

EXAMPLE 4A

[0048] The following formulation is prepared:

Ingredients	Weight per coated tablet (mg)	% per coated Tablet
Metformin HCL	1000.00	86.2
Polyvinylalcohol (PVAe)	34.00	2.9
Colloidal Silicon Dioxide (Aerosil® 200)	24.8	2.2
Purified Water*	0	0
Crospovidone (Kollidon CL®)	39.2	3.4
Glyceryl Behenate (Compritol® 888 ATO)	22.0	1.9
Total (dry weight)	1058.8	96.6

* Evaporates during granulation

[0049] The Metformin HCl and a portion of the colloidal silicon dioxide (20mg (1.8%)) are placed in a fluidized bed apparatus. An aqueous polyvinylalcohol solution (at 4.59% by weight) is sprayed to get granules. The apparatus used for the granulation is a Glatt GPCG60, operated with the following parameters:

Process Air (cfm)	600 ± 200 cfm
Liquid flow (g/min)	175 ± 100 g/min
Inlet temperature	65 ± 15°C
Atomization air pressure	3.5-5.5 bar

[0050] The granules obtained are subsequently dried and passed through a 1 mm mesh sieve. The glyceryl behenate, crospovidone and remaining colloidal silicon dioxide is added to sized granules and the resulting mixture is blended in a drum nixer (Turbula T2C, Bachoffen, Switzerland). The resulting mixture is pressed into tablets (7mm diameter and 7mm curvature) with an average hardness being between 60 and 120N. The resulting tablet cores are then coated with the following formulation:

Ingredients	Weight per Coated Tablet (mg)	% per Coated Tablet
Tablet Cores	1058.8	96.6
Ethylcellulose (Ethocel PR100)	21.3	1.8
Povidone USP (Kollidon 90F)	10.7	0.9
Dibutyl Sebacate	8.0	0.7
Pure Ethyl Alcohol**	0	0
Isopropyl Alcohol**	0	0
Total (dry weight)	1160	100

** Evaporates during tablet coating.

[0051] The Ethocel, povidone and dibutyl sebacate are dissolved in a mixture of pure ethyl alcohol and isopropyl alcohol. The coating solution is then sprayed onto the tablet cores in a Labcoat III O'Hara Pan Coater, with the following spray parameters:

Process air (cfm)	800 ±150 cfm
Liquid flow (g/min)	100-220 g/min
Inlet temperature	40 ± 8 °C
Atomization air pressure	30 ± 10 PSI
Pattern air pressure	20-40 PSI

The tablet cores are coated until about 40mg weight gain is achieved per tablet core. Stability results show that the metformin composition of this example is stable.

EXAMPLE 4B

[0052] The following formulation is prepared according to the same process as Example 4A:

Ingredients	Weight per coated tablet (mg)	% per coated Tablet
Metformin HCL	750.00	85.2
Polyvinylalcohol (PVAe)	25.5	2.9
Colloidal Silicon Dioxide (Aerosil® 200)	18.6	2.1
Purified Water*	0	0
Crospovidone (Kollidon CL®)	29.4	3.4
Glyceryl Behenate (Compritol® 888 ATO)	16.5	1.9
Total (dry weight)	840.00	95.5

* Evaporates during granulation

[0053] The tableted cores are then coated with the following coat formulation by the same process described in Example 4A:

Ingredients	Weight per Coated Tablet (mg)	% per Coated Tablet
Tablet Cores	840.0	95.5
Ethylcellulose (Ethocel PR100)	21.3	2.4
Povidone USP (Kollidon 90F)	10.7	1.2
Dibutyl Sebacate	8.0	0.9
Pure Ethyl Alcohol**	0	0%
Isopropyl Alcohol**	0	0%
Total (dry weight)	880.0	100%

** Evaporates during tablet coating.

EXAMPLE 5

[0054] The dissolution profiles of the tablets in Examples 1A-4 are determined under the following dissolution conditions:

- Medium: 900 ml phosphate buffer pH 6.8
- Method: 75 rpm USP Apparatus I.

The results are presented below as a % of the total metformin in the tablet:

Time (hour)	2	4	8	12
Example 1A	13.8	32.9	69.3	91.9
Example 1B	23.8	53.2	92.3	100.0
Example 2A	23.8	51.0	89.4	100.0
Example 2B	11.5	29.1	67.3	92.3
Example 3A	29.1	51.9	80.2	91.8
Example 3B	53.6	84.6	100	N/A

Time (hour)	0	1	2	3	4	6	8	10	12
Example 4, lot 3508	0	15.93	33.55	32.9	63.72	85.5	95.77	99.07	100.05
Example 4, lot 3517	0	13.30	29.35	53.2	57.27	79.98	92.98	98.32	100.13
Example 4, lot 3541	0	11.53	26.77	51.0	53.03	75.5	89.55	95.93	98.43

[0055] The dissolution profiles of the extended release products prepared as in Example 4 is shown in FIG. 1 for the three lot numbers.

EXAMPLE 5A

[0056] The dissolution profiles of the tablets in Examples 4B and 4C are determined under the following dissolution conditions:

Medium: Di H_2O

Method: 50 rpm US Apparatus I at 37°C

The results are presented below as a % of the total metformin in the tablet:

Example 4A		Example 4B	
Time (hr)	Mean % metformin released	Time (hr)	Mean % metformin released
0	0	0	0
0.5	10	0.5	9
1	20	1	18
2	36	2	36
3	51	3	52
4	63	4	66
5	74	5	77
6	83	6	85
7	89	7	92
8	94	8	96
9	97	10	99
10	99	12	101
11	100		
12	101		
13	101		
14	101		
15	101		
16	101		
17	102		
18	102		
19	102		
20	102		
21	102		
22	102		
23	102		
24	102		

[0057] The dissolution profiles of the extended release products prepared as in Example 4A and 4B is shown in FIG. 2 and FIG. 3 respectively.

(COMPARATIVE) EXAMPLE 6

[0058] One advantage of the invention is that it provides sustained release tablet with vastly improved dissolution properties without the need for a coating having preformed pores. In order to illustrate the advantage of the coatings according to the invention which do not require preformed pores to provide the desired dissolution profile, Applicants showed that cores of the present invention when coated with a semi-permeable membrane as taught in US Patent No. 6,099,859, but without pre-formed mechanical or laser drilled pores in the coat, long periods of time of over 300 minutes are required before the metformin starts to be released. Applicants prepared and tested tablets containing a core according to the invention with a coating prepared according to the '859 patent, but without pores formed therein. The cores of the present invention (with or without crospovidone) were coated with the semi-permeable formulation as taught in the '859 patent but did not have a mechanical or laser drilled hole or pore in the semi-permeable membrane. The dissolution profile of such a tablet is shown in FIG. 4. As shown in FIG. 4, no metformin was measurably released for the first 350 – 500 minutes depending on whether the core had crospovidone. The rather rapid release of metformin seen after this time period is believed to be the result of tablet disintegration.

[0059] The invention is not limited to the specific embodiments described above but can be varied within broad limits by the skilled artisan.